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In re Application of Bateman et al.

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Serial Number 10/633,702

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For: MASS SPECTROMETER

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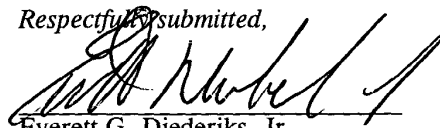
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Everett G. Diederiks, Jr.

Attorney for Applicant

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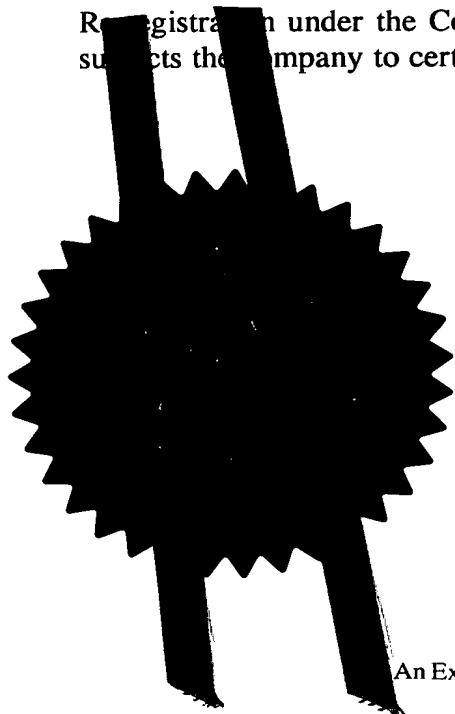
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GB0218139.4

By virtue of a direction given under Section 30 of the Patents Act 1977, the application is proceeding in the name of:-

MICROMASS UK LIMITED
Incorporated in the United Kingdom
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Simonsway
MANCHESTER
M22 5PP
United Kingdom

ADP No. 07649676002

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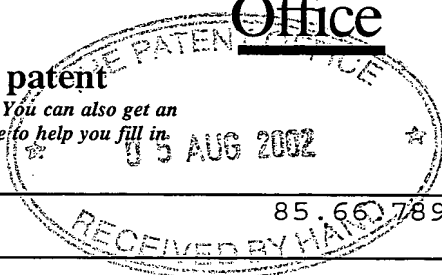
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Request for grant of a patent

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1. Your reference	85.66278936		
2. Patent application number (The Patent Office will fill in this part)	05 AUG 2002		0218139.4
3. Full name, address and postcode of the or of each applicant (underline all surnames)	Micromass Limited Floats Road Wythenshawe Manchester M23 9LZ		
Patents ADP number (if you know it)	06996102001		
If the applicant is a corporate body, give country/state of incorporation	United Kingdom	06AUG02 E738661-2 D00027 P01/7700 0.00-0218139.4	
4. Title of the invention	Mass Spectrometer		
5. Name of your agent (if you have one)	Frank B. Dehn & Co.		
"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	179 Queen Victoria Street London EC4V 4EL		
Patents ADP number (if you know it)	166001	✓	
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11. I/We request the grant of a patent on the basis of this application.

Signature  Date 5 August 2002

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P.M. Jeffrey
01273 244200

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Stationary and Travelling Wave Ion Guide used in conjunction with a pulsed source of ions for separating and trapping ions with different masses

INTRODUCTION

A common form of tandem mass spectrometry (MS/MS) involves transmitting ions from an ion source through a mass filter set to transmit ions of the required mass/charge (m/z) ratio, through a gas collision cell where the ions are induced to fragment, and into a mass analyser for mass analysis of the fragments. The mass filter is typically a quadrupole mass filter, or other multipole ion guide. The mass analyser may typically be a quadrupole mass filter, a time-of-flight mass analyser, a linear or 3-D quadrupole ion trap, a magnetic sector or an FT-ICR mass analyser. Such tandem mass spectrometers are well known and widely used. When used to identify or quantify a single component in a sample they can have a high duty cycle. However, for some applications where there is a need to identify or quantify many different components in the sample their duty cycle can be quite poor. This is because while ions of one particular component are being transmitted through the mass filter for fragmentation and subsequent analysis ions from other components in the sample are being discarded. The duty cycle decreases as the number of components to be analysed increases.

A method of reducing this problem is described in patent applications GB.2,363,249 and US 2002/0063206 where ions from a number of different components are simultaneously transmitted for fragmentation and subsequent analysis. Here daughter or product ions are associated with their parent ions when their respective elution profiles match. Matching daughter ions to parent ions becomes more difficult as the number of different components in the sample increases. This method becomes quite difficult to implement when the number of components to be analysed at any one time exceeds ten.

Another method of addressing this problem is proposed in patent application WO 01/15201. Here the ions from a multitude of components are stored in a mass selective ion trap device. Ions of a single component of interest may then be selectively extracted and transferred to a second ion trap whilst the remaining ions continue to be stored in the first ion trap. The ions transferred to the second trap may now be fragmented and mass analysed. The process of mass selective ion extraction, fragmentation and analysis is now repeated with ions of a second component of interest. In principle this may be repeated as many times as required.

Another method of addressing this problem is to make use of more and more means of separation of the components of a complex mixture with the objective of only presenting one component at a time to the ion source of the mass spectrometer. A number of different systems incorporating multiple stages of various combinations of different types of chromatography, electrophoresis and other means of separation have been interfaced to tandem mass spectrometers with the objective of analysing a complex mixture by presenting one component, or very few components, at any one moment in time to the ion source of the mass spectrometer. In some arrangements it has been necessary to collect "fractions" from one or more means of separation, store the fractions, and then analyse each "fraction" in turn by further means of separation interfaced to the tandem mass spectrometer.

Another means of separation to those of chromatography and electrophoresis is that of ion mobility mass spectrometry in which ions may be separated according to their mobility, or some property related to their mobility. For example, in the Field Asymmetric Ion Mobility Separator (FAIMS) device ions are separated according to their rate of change of mobility with electric field strength. The ion mobility spectrometer separates ions and therefore, if included within the apparatus, would normally be positioned after the ion source and not before it. The ion mobility spectrometer can be used at atmospheric pressure, or at pressures down to ~ 0.01 milli-bar. However, it cannot be used at the pressures at which a mass analyser would normally operate since the ions travelling in an ion mobility spectrometer must be subject to collisions with gas molecules whereas ions travelling through a mass analyser preferably are not subject to any collisions with gas molecules. If the source of ions is at atmospheric pressure the ion mobility spectrometer may be positioned between the ion source and mass analyser, either at atmospheric pressure or at an intermediate pressure between that of the ion source and that of the mass analyser. Such an arrangement is described in patent application US 2002/0070338. Here ions are contained in an RF multi-pole rod set ion guide in the presence of a collision gas, and separated according to ion mobility by applying a linear axial DC electric field. According to one embodiment the multi-pole rod sets are segmented such that, after separation according to mobility, the linear axial DC electric field can then be switched to a different axial DC electric field in which a series of potential wells are formed for trapping ions. Ions of different mobility are at different positions when the field profile is switched, and are therefore trapped in different wells. The ions in each well can be separately released for mass analysis, or fragmentation and mass analysis. This device is, in effect, a means of "fraction" collection for an ion mobility separator, and provides another method of analysing a number of components in a complex mixture, one at a time, by tandem mass spectrometry.

In this invention is described a means of "fraction" collection of ions from a mass analyser. Ions are collected and stored according to their mass/charge (m/z) ratios. The ions are separated according to their m/z values, trapped in a series of ion trapping potential wells, and stored for subsequent analysis. The ions in one or more potential wells may be subsequently released for mass analysis, for fragmentation and mass analysis, or for mass selection, fragmentation and mass analysis.

STATE OF THE ART

Radio frequency (RF) ion guides are commonly used for confining and transporting ions. All such ion guides use an arrangement of electrodes with an RF voltage applied between neighbouring electrodes such as to produce an inhomogeneous RF field. In such fields ions can behave as though they are contained within a potential well or valley, often referred to as a pseudo-potential well or valley. This pseudo-potential well can be arranged to confine ions, and may be effectively used to transport ions by acting as an ion guide.

The RF ion guide can still function efficiently as an ion guide even at quite high pressures, where ions are likely to undergo frequent collisions with residual gas molecules. The collisions with gas molecules may cause the ion to scatter and lose energy, but the pseudo potential well generated by the RF ion guide still acts to confine the ions.

As a consequence of this ability to transport ions at relatively high pressures, the RF ion guide is the preferred type of ion guide for a number of applications in mass spectrometry apparatus. In particular it is used in "gas collision cells" in which relatively low energy ions (i.e. ions with energies between 10 and 1000 eV) undergo multiple collisions with gas molecules to induce ion

fragmentation. Also it is used to transport ions through chambers at intermediate pressures (0.001 ~ 10 mbar) from an ion source in a chamber at high pressure (e.g. an atmospheric pressure ion source) to a mass analyser in a chamber at very low pressure. Ions can be efficiently transported despite undergoing many collisions with gas molecules causing the ions to be scattered and to lose energy.

As has been already mentioned, when an ion collides with a gas molecule it may get scattered and lose kinetic energy. If the ion undergoes a large number of collisions, perhaps more than 100 collisions, the ion will lose all its forward kinetic energy. The ions will now have a mean energy equal to that of the surrounding gas molecules. They will now appear to move randomly within the gas due to continuing random collisions with gas molecules.

A known means for driving ions through an RF ion guide at intermediate pressures is the application of an axial electric field along the device. The axial electric field may be applied in a number of ways. For example, axial electric fields may be applied to ion guides using multi-pole rod sets by the use of segmented rods with a DC voltage between successive rods, by the use of inclined rods, or by the use of resistive rods with a DC voltage gradient along their length. Axial fields may be applied to ion guides using stacked ring sets by applying a DC voltage to successive rings or groups of rings. Axial fields may also be applied by the use of additional electrodes, usually in the form of cylinders, external to the ion guide such that some of this axial field penetrates into the ion guide itself. In all these cases the axial electric field causes the ions to accelerate forwards after each collision with a gas molecule. A weak field, in the region of 0.1 to 1 volt/cm, is adequate at pressures between 0.001 and 0.01 mbar. At higher pressures higher field strengths can be used.

An alternative means using AC axial fields in an RF ion guide has been described in patent applications [MM 1071 and MM 1153 – yet to be published]. Here the axial field profile is such as to form one or more potential wells and/or potential hills that move along the length of the RF ion guide to form a travelling wave. The travelling wave device requires that the RF ion guide be segmented axially such that DC potentials can be applied independently to each segment and these potentials can be controlled temporally to produce a wave along the device to impel ions. For example, the ion guide may take the form of a segmented multi-pole rod set or a ring stack.

The use of a travelling wave ion guide with a pulsed ion source, such as a laser ablation source or MALDI source, or with ions released in the form of a pulse from an ion trap, is described in patent application [MM 1156 – yet to be published]. Here the ions pass through a region wherein they are arranged into some sequence before reaching the travelling wave ion guide. For example, if the ions from the ion source are accelerated to a given energy and are allowed to pass through a field free region at low pressure then ions of different masses will travel at different velocities. Hence ions of lighter mass that have higher velocities will arrive at the travelling wave device before heavier ions that have lower velocities. On arrival at the travelling wave ion guide ions will be collected in groups according to their mass/charge ratio and transported through the travelling wave device as a discrete group. So ions will emerge at the exit of the travelling wave device in packets consisting of ions with mass/charge ratios falling within restricted ranges.

THE NEW INVENTION

Ions are released from an ion source, or from a device for trapping or storing ions, pass through a region wherein they are separated according to their mass/charge (m/z) ratios before reaching a segmented RF ion guide. In the RF ion guide the ions are collected in groups according to their mass/charge ratios in potential wells along the axis of the RF ion guide. Here the ions are stored and may be released for subsequent analysis.

In a preferred embodiment ions are released from a pulsed ion source, such as a laser ablation source or MALDI source, or released in a pulse from a device for trapping or storing ions, pass through a region wherein they are arranged into a sequence according to their mass/charge (m/z) ratios before reaching a segmented RF ion guide. For example, if the ions from the ion source are accelerated through a constant potential difference, such as to gain a constant energy, and are allowed to pass through a region at low pressure then ions of different masses will travel at different velocities. Hence ions of lighter mass that have higher velocities will arrive at the RF ion guide before heavier ions that have lower velocities. In the RF ion guide the ions may be collected in potential wells along the axis of the RF ion guide. Hence, the ions are collected in groups according to their mass/charge. The ions are stored in the potential wells and may be released for subsequent analysis. Figure 1 shows an example of such an arrangement.

The separation of ions according to mass/charge ratio before arrival at the RF ion guide can take place in a field free region, or in an ion guide. The ion guide preferably is an RF ion guide, such as a multi-pole rod set, with zero axial DC electric field. Alternatively the RF ion guide may be a ring stack with zero average axial DC electric field. Other ion guides, such as those employing guide wires, may also be used.

In one embodiment, the ions will arrive within the RF ion guide, which is segmented, and will occupy positions along the length of the ion guide according to their mass/charge ratios. Ions with the lower mass/charge ratios will have travelled further. At the appropriate time a series of voltages will be applied to certain elements of the segmented ion guide such as to create a series of potential wells. For example, a sequence of potentials may be applied to a first set of elements along the ion guide to form a potential hill, and this sequence repeated at regular intervals along the length of the ion guide such as to create a repeating pattern of potential wells separated by potential hills. If preferred the potential wells may be spaced at non-regular intervals. The height of the potential hills will be sufficient to trap ions positioned between neighbouring potential hills, and so ions will be trapped and stored in the different potential wells along the length of the ion guide according to their mass/charge ratios. Ions may oscillate within each potential well but, if required, may be subsequently dampened by the introduction of gas to damp the ion motion. The presence of gas will result in collisions between the ions and gas molecules, and the ions will gradually lose energy until their energies are reduced to that of the damping gas. As the ions lose energy they will fall towards the lowest points within the potential wells. The ions may now be stored in the potential wells until released for subsequent analysis.

Figure 2 illustrates the distribution of the range of m/z values that may be collected and stored in each potential well for such an arrangement. In this example the length of the first ion guide (L1) is 150 mm and the length of the second ion guide (L2) is also 150 mm. The second ion guide contains 10 potential wells spaced at regular intervals of 15 mm. The ion energy is 3 eV, and the waveform profile along the second ion guide is switched on 315 micro-second after the pulse of

ions are accelerated from the source. In this illustration the range of m/z values collected in the first potential well is m/z 700 to m/z 800. In the last potential well the range of m/z values collected is m/z 2100 to m/z 2550.

In another embodiment the ions will arrive at the RF ion guide on which a travelling wave has been superimposed. As the ions arrive at the entrance to the RF ion guide they will coincide with the appearance of a potential well travelling in the same direction as the ions. These ions will travel with this potential well. Ions with progressively higher m/z values will arrive at progressively later times and will also travel with this potential well until the point where a potential hill now emerges, also travelling in the same direction as the ions. Ions arriving after this time will be too late to be collected within the preceding potential well and will now be collected and travel with the following potential well. This sequence of events will repeat itself as long as ions continue to arrive. A few steps in this sequence are illustrated in figure 3. Hence each potential well will collect a series of ions with a range of m/z values higher than its predecessor. As described before ions may oscillate within each potential well but, if required, may be subsequently dampened by the introduction of gas to damp the ion motion.

If preferred the width of the potential wells may be varied such as to vary the range of m/z values collected in each well. Figure 4 illustrates how the collection of ions might be distributed according to their m/z ratios in such a device where the travelling wave has a constant velocity and a constant wavelength. In this example the lengths of the first and second ion guides (L1) and (L2) are both 150 mm. The travelling wave has a wavelength of 15 mm, and wave cycle time of 30 μ -second. The ion energy is 1 eV and the diagram shows the range of m/z values collected in each well over the period from 300 μ -sec to 600 μ -sec from the release of ions from the source. Ions collected in the first well (after 300 μ -sec) have m/z values in the range 780 to 920. Ions collected in the last well (up to 600 μ -sec) have m/z values in the range 2500 to 2790.

In a preferred embodiment the velocity of the travelling wave will progressively slow down to match that of the ions arriving at the RF ion guide. For example, if the ions from the ion source are accelerated to a given energy and are allowed to pass through a field free region at low pressure then ions of different masses will travel at different velocities. Ions with lower m/z values will have higher velocities and will arrive at the travelling wave device before ions with higher m/z values that have lower velocities. On arrival at the travelling wave ion guide ions will be collected in groups according to their mass/charge ratio and transported through the travelling wave device as a discrete group. Ideally the velocity of the travelling wave should match that of the arriving ions, and hence its velocity should decrease as ions with progressively higher m/z values arrive at the ion guide. Likewise the velocity of the ions already collected in the travelling potential wells should also decrease to match that of the travelling wave. As described before ion motion may be dampened by the presence of a buffer gas. Under the right conditions the ion velocity may be made to decrease at the same rate as that of the travelling wave.

In the following analysis of such an arrangement it is assumed that ions are released from a pulsed ion source, for example a laser ablation or MALDI ion source, or from an ion trap. Ions then travel through an RF ion guide, with zero axial electric field, and on to an RF ion guide with superimposed travelling wave. The ion guide with zero axial electric field is at low pressure (less than 0.0001 mbar) and the travelling wave ion guide is at intermediate pressure (between 0.001 and 1 mbar).

Let the distance in meters from the ion source to the entrance to the travelling wave ion guide be $L1$ meters, and the length of the travelling wave ion guide be $L2$ meters. Also, let the ions be accelerated through a voltage difference of $V1$ at the ion source such that they have energy of $(z.e.V1)$ electron volts.

Then, for ions of mass/charge ratio $= m/z$, the arrival time, $T1$, (in μsec) for ions, after their pulsed release from the source or ion trap, to reach the entrance to the travelling wave ion guide is:

$$T1 := 72 \cdot L1 \cdot \sqrt{\frac{m}{z \cdot e \cdot V1}} \quad (1)$$

The velocity (v) of these ions will be:

$$v := \frac{L1}{T1} \quad (2)$$

The travelling wave device may be used at intermediate pressures between 0.0001 and 100 mbar, but preferably between 0.001 and 1 mbar, for which the gas density will be sufficient to impose a viscous drag on the ions. The gas at these pressures will appear as a viscous medium to the ions and will act to slow the ions.

If it is arranged that the velocity (v) of the travelling wave is equal to that of the ions as they arrive at the entrance to the travelling wave ion guide, then $v = v$. Since the velocity of the ions arriving at the entrance to the ion guide is inversely proportional to elapsed time ($T1$) from release of ions from the source or ion trap, then also the velocity of the travelling wave must also decrease with time in the same way. Since the wave velocity (v) is equal to λ/T (where λ is the wavelength and T is the cycle time of the waveform), then it follows that the cycle time (T) should vary in proportion to the elapsed time ($T1$). In other words, for the wave velocity to always equal the velocity of the ions arriving at the entrance to the travelling wave ion guide, the wave cycle time should increase linearly with time.

Since the wave velocity (v) will be continuously slowing it may be expected that the ions would travel on ahead of the wave. However, the viscous drag resulting from frequent collisions with gas molecules will prevent the ions from building up excessive velocity. Consequently the ions will tend to ride on the travelling wave rather than run ahead of the wave and execute excessive oscillations within the travelling potential wells.

If, in time δt , the ions travel distance δl within the ion guide, where

$$\delta l := v \cdot \delta t$$

Then, if the time at which the ions reach the exit the travelling wave ion guide is $T2$, then the distance (ΔL) travelled within the ion guide is:

$$\Delta L := \int_{T1}^{T2} v \, dt$$

$$\Delta L := \int_{T1}^{T2} \frac{L1}{t} dt$$

$$\Delta L := L1 \cdot (\ln(T2) - \ln(T1))$$

$$\Delta L := L1 \cdot \ln\left(\frac{T2}{T1}\right) \quad (3)$$

But the length of the ion guide is L2; therefore $\Delta L = L2$ and therefore:

$$L2 := L1 \cdot \ln\left(\frac{T2}{T1}\right)$$

$$T2 := T1 \cdot e^{\left(\frac{L2}{L1}\right)} \quad (4)$$

Hence, the velocity of the ions (v_x) as they reach the end of the travelling wave ion guide is equal to that of the travelling wave at that time, and therefore is:

$$v_x := \frac{L1}{T2} \quad (5)$$

$$v_x := \frac{L1}{T1} \cdot e^{-\left(\frac{L2}{L1}\right)}$$

$$v_x := v \cdot e^{-\left(\frac{L2}{L1}\right)} \quad (6)$$

Since the energy of the ions at the entrance to the ion guide is $E1 = z \cdot e \cdot V1$

Then,

$$E1 := \frac{1}{2} \cdot m \cdot v^2$$

If the energy of the ions at the exit of the ion guide is E2,

Then,

$$E2 := \frac{1}{2} \cdot m \cdot v_x^2$$

$$E2 := \frac{1}{2} \cdot m \cdot v^2 \cdot e^{-2\left(\frac{L2}{L1}\right)}$$

$$E2 := E1 \cdot e^{-2\left(\frac{L2}{L1}\right)} \quad (7)$$

Hence for such an arrangement where the wave velocity is matched to that of the arriving ions it follows that for ions within the travelling wave ion guide their velocity and energy must decay exponentially with the distance travelled into the ion guide.

The gas in the travelling wave ion guide will result in frequent ion-molecule collisions, which in turn will cause the ions to lose kinetic energy. In the presence of an RF confining field both the axial and radial kinetic energies will be reduced. Furthermore, the axial and radial energies decay approximately exponentially with distance travelled into the ion guide (J. Am. Soc. Mass Spectrom., 1998, 9, pp 569-579). From computer simulations the authors estimate kinetic energies in axial and radial directions reduce to 10% whilst passing through a nitrogen gas pressure-distance product of approximately 0.1 mbar-cm. Hence, both the wave velocity and the ion kinetic energies will decay exponentially. These two exponential decay rates may be arranged to be approximately the same by appropriate choice of collision gas molecular mass and pressure.

As the ions enter the travelling wave ion guide they will be grouped such that each group contains only ions within a limited range of mass/charge ratios, and each group will have ions with mass/charge ratios higher than those of the preceding group. After the last ions of interest have entered the ion guide the travelling wave can be halted and the ions will remain trapped in their respective potential wells according to their m/z values. Any further damping of ion motion that may be required will take place for as long as the buffer gas pressure in the device is maintained. Ions may now be stored and released for subsequent analysis when required.

Ions may be released from the series of potential wells either from the end to which they were travelling or from the end through which they entered the ion guide. In the former case the ions will be released in increasing order of m/z value starting with those with the lowest m/z values stored. In the latter case ions are reversed in direction to be released from the end of the device through which they entered. In this case ions will be released in decreasing order of m/z value starting with those with the highest m/z values stored. Ions may be released by lowering the potential hill or barrier retaining the ions and accelerating the ions out in the required direction. Alternatively, ions may be released by moving the waveform along one wavelength in the required direction. This will push out the ions in the group nearest the exit and at the same time move all the other ions in their respective groups one wavelength nearer to the exit.

PREFERRED EMBODIMENT

The device described here provides a means of efficiently allowing a large number of components from a mixture of components to be analysed in a tandem mass spectrometer by means of collision induced fragmentation and subsequent mass analysis of the fragment ions. The device allows the components to be separated, or partially separated, into groups according to their m/z values, stored in a series of separate potential wells, and subsequently analysed in groups, one group at a time. Furthermore, if required, ions of one m/z value from each group may be first selected before fragmentation and mass analysis. Figure 5 shows a block diagram illustrating how the device may be used as part of a complete system for carrying out such analyses.

In this configuration the ion source (A) is preferably a pulsed ion source, such as a matrix assisted laser desorption and ionisation source (MALDI). A pulse of ions from the source would be collected and cooled in the RF ion trapping device (B). This could be a segmented RF ion guide that also functions as an ion trap by virtue of being able to be programmed with different DC potentials along its length. When used to trap ions it may be programmed to have an axial potential well at some point along its length. It may be a segmented multi-pole rod set, or a stacked ring set, or a stacked plate set in the form of a sandwich, or some combination of these devices. It is not necessary for this device to be a mass selective ion trap, such as a quadrupole ion trap. This device for trapping ions may use a buffer gas for cooling the ions. This may help to improve the trapping efficiency of this device, and also cool energetic ions from the ion source.

If it is only required to mass analyse the trapped ions the ions may now be released in the direction of the ion guide (E) and the mass analyser (F). The mass analyser may be a quadrupole mass filter, a linear or 3-D quadrupole ion trap, a time-of-flight mass analyser, an FT-ICR mass analyser, or a magnetic sector. Preferably the mass analyser is an orthogonal acceleration time-of-flight mass analyser, or an orthogonal acceleration time-of-flight mass analyser used in conjunction with a synchronised travelling wave ion guide as described in patent application (MM 1156 – yet to be published) to maximise its duty cycle throughout the mass range to be recorded.

If on the other hand it is required to fragment and analyse a number of different ions from the mixture of ions released from the ion source (A) and collected in the ion trapping device (B) the ions may then be released from the ion trapping device (B) in a single pulse in the direction of the quadrupole ion guide (C) and ion collection and storage device (D). The quadrupole RF ion guide (C) would allow ions to be separated according to their m/z values, and the ion collection and storage device (D) would allow ions to be collected and stored in groups according to their m/z values as already described. Preferably the ion collection and storage device (D) would use a progressively slowing travelling wave as already described. Ions may now be released from the series of potential wells in the ion storage device (D) in reverse order starting with ions with the highest m/z values. Ions from the first group would be ejected in the reverse direction back through the quadrupole RF ion guide (C) and into the ion trapping device (B). The quadrupole RF ion guide (C) may be operated in the non-resolving mode (RF only supplied) such as to transmit all the ions within that group. Alternatively, the quadrupole ion guide (C) may now be operated in the resolving mode (RF and DC supplied) such as to transmit ions with just one, or with a limited range, of m/z values. In the ion trapping device (B) the ions may be fragmented by collision activation with the buffer gas. The fragment ions may now be trapped in the ion trapping device (B). The fragment ions are now released in the direction of the ion guide (E) and the mass analyser (F) for mass analysis as already described above.

This procedure may be repeated for the next group of ions from the next potential well in the ion collection and storage device (D). This may be repeated again and again until all the groups of ions have been analysed, or ions of selected m/z value within each group have been analysed. Hence the ion collection and storage device (D) behaves as “fraction” collection device for ions with different m/z values, and allows many different fragmentation and mass analyses to be performed from the original mixture of ions.

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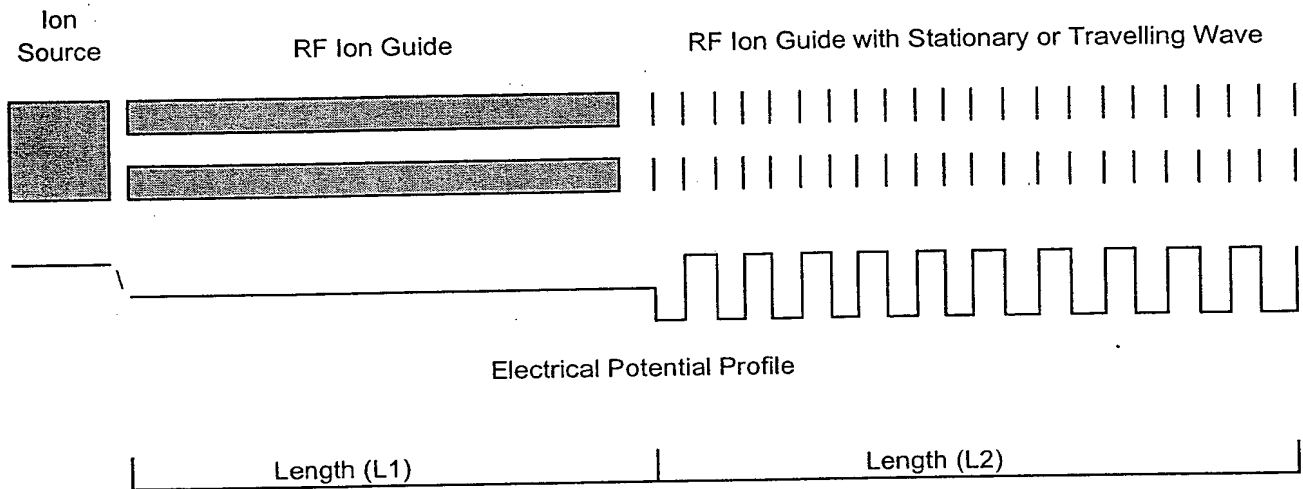


Figure 1

Direction of ion travel ---->

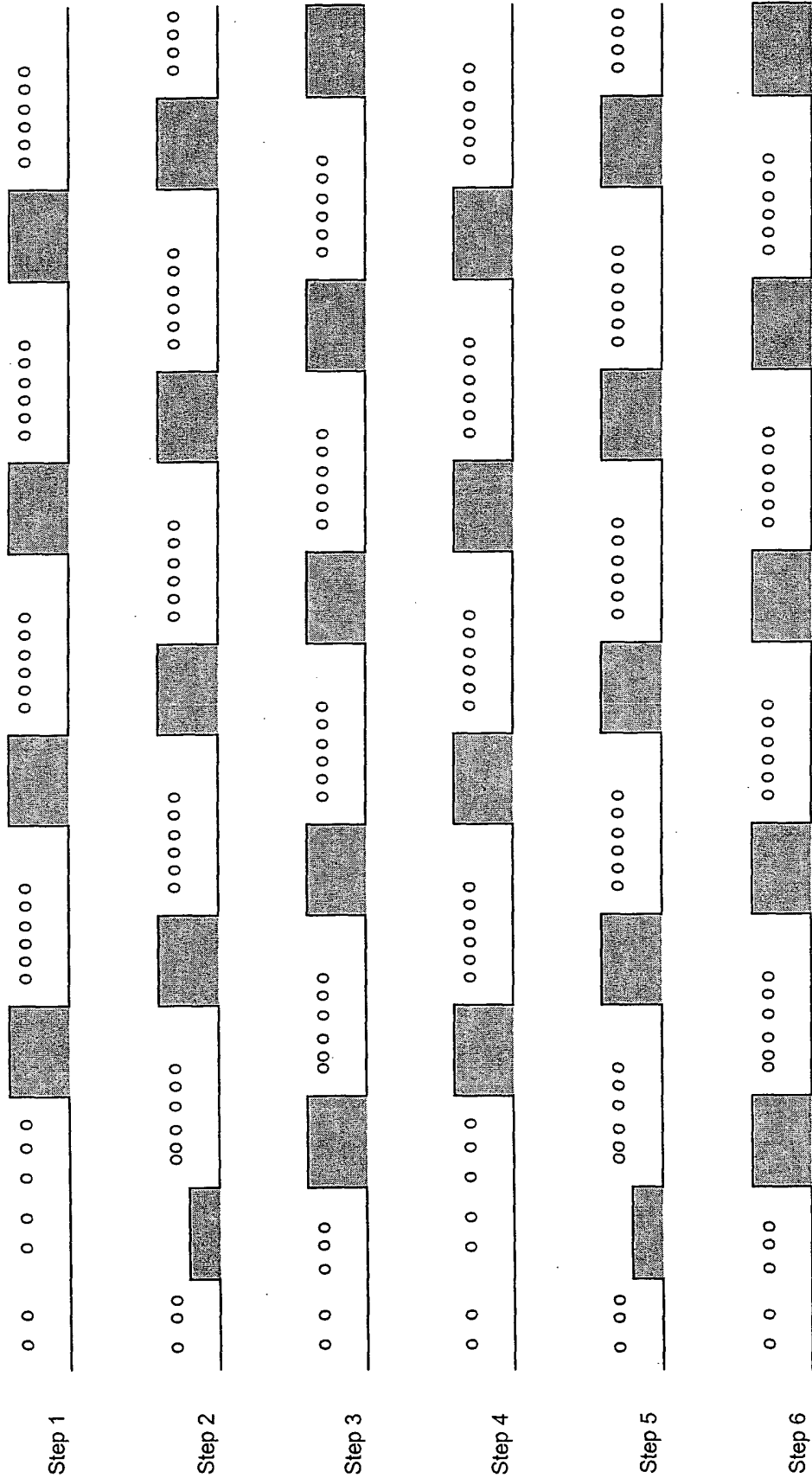


Figure 3

Mass ranges within each well

$T(n)$, 330, 360, 390, 420, 450, 480, 510, 540, 570

Ion guide division (micro-sec)

515

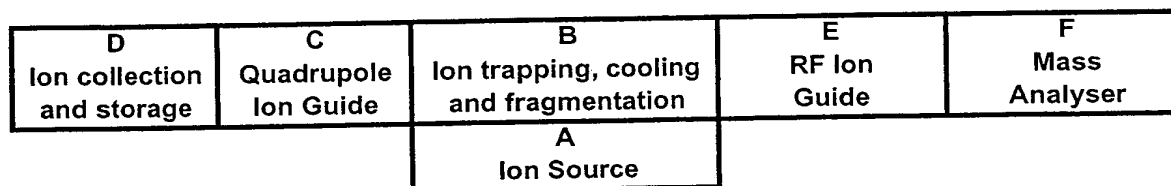


Figure 5

Serial No: 101633,702

Filed: August 5, 2003

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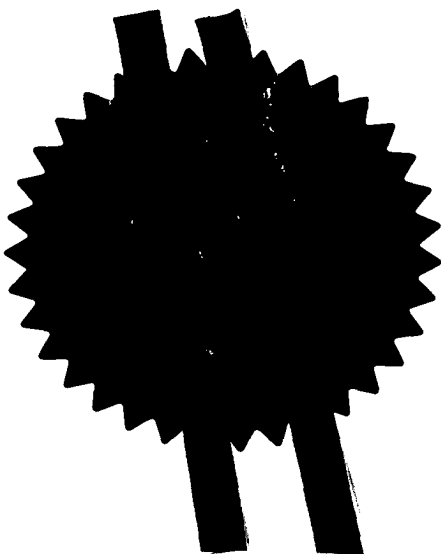
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4. Title of the invention	Mass Spectrometer		
5. Name of your agent (if you have one)	Frank B. Dehn & Co.		
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SECTION 30(1)(a) APPLICATION FILED 02-06-03
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TWIG5

MASS SPECTROMETER

5 The present invention relates to a mass spectrometer and a method of mass spectrometry.

 A common form of tandem mass spectrometry (MS/MS) involves transmitting ions from an ion source through an mass filter arranged upstream of a collision cell. The
10 mass filter is set to transmit only ions having a specific mass to charge ratio to the gas collision cell. Ions entering the collision cell are induced to fragment. The fragment ions which exit from the collision cell are then mass analysed by a mass analyser
15 arranged downstream of the collision cell.

 The mass filter upstream of the collision cell is typically a quadrupole mass filter and the mass analyser downstream of the collision cell is typically a quadrupole mass analyser, a Time of Flight mass
20 analyser, a linear or 3-D quadrupole ion trap, a magnetic sector mass analyser or an FTICR mass analyser.

 A problem with such known tandem mass spectrometers is that in applications where there is a need to identify or quantify many different components from a
25 sample the duty cycle can be relatively poor. This is because whilst some ions having a specific mass to charge ratio are being transmitted through the mass filter upstream of the collision cell, other ions from the sample are being attenuated by the mass filter. The
30 duty cycle and hence sensitivity further decreases as the number of components to be analysed increases.

 According to an aspect of the present invention there is provided a mass spectrometer as claimed in claim 1.

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According to a preferred embodiment there is provided a means of fraction collection of ions. Ions which have been separated according e.g. to their mass to charge ratios are trapped and stored in a series of ion trapping potential wells along the length of the ion trap for subsequent analysis. The ions in one or more potential wells may be subsequently released for mass analysis, for fragmentation and mass analysis, or for mass selection, fragmentation and mass analysis.

Radio frequency (RF) ion guides are commonly used for confining and transporting ions and comprise an arrangement of electrodes with an RF voltage applied between neighbouring electrodes so that an inhomogeneous RF field is provided. Ions are therefore radially confined within the ion guide.

The RF ion guide can still function efficiently as an ion guide even at relatively high pressures where ions are likely to undergo frequent collisions with residual gas molecules. The collisions with gas molecules may cause the ion to scatter and lose energy but the pseudo-potential well generated by the RF ion guide acts to radially confine the ions within the ion guide.

Various embodiments of the present invention will now be described, by way of example only, and with reference to the accompanying drawings in which:

Fig. 1 shows a preferred embodiment;

Fig. 2 shows the distribution of ions according to their mass to charge ratios; and

Fig. 3 shows the distribution of ions according to their mass to charge ratios.

A preferred embodiment will now be described in relation to Fig. 1. Ions are released from a pulsed ion

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source 1 such as a laser ablation ion source or a MALDI ion source or alternatively are released in a pulse from an ion trap (not shown). The ions are then accelerated through a constant potential difference so that they gain a constant energy and are then allowed to pass through a drift region 2 which maintained at a relatively low pressure so that ions of different masses will travel at different velocities.

The ions therefore become temporarily dispersed according to their mass to charge ratios. The ions then exit the drift region 2 and enter a segmented RF ion guide 3. Ions of lighter mass will have acquired higher velocities in the drift region 2 and hence will arrive at the segmented RF ion guide 3 before heavier ions which will have corresponding lower velocities. In the segmented RF ion guide 3 the ions are collected in potential wells along the axis of the RF ion guide 3. Accordingly, ions are collected in groups according to their mass to charge ratio. The ions are stored in the potential wells and may be released for subsequent analysis.

The separation of ions according to mass to charge ratio before arrival at the segmented RF ion guide 3 can take place in a field free region or in an ion guide 2. The ion guide 2 is preferably an RF ion guide such as a multi-pole rod set with zero axial DC electric field. Alternatively, the ion guide 2 may comprise a ring stack ion guide with zero average axial DC electric field. Other ion guides such as those employing guide wires may also be used according to less preferred embodiments.

According to a first main embodiment ions arrive within the RF ion guide 3 and occupy positions along the length of the ion guide 3 according to their mass to

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charge ratios. Ions with the lower mass to charge ratios will have travelled further into the ion guide 3 than ions having higher mass to charge ratios. At an appropriate time a series of voltages is then applied to certain elements of the segmented ion guide 3 so as to create a series of potential wells along the length of the ion guide 3. For example, a sequence of potentials may be applied to a first set of elements along the ion guide 3 so as to form a potential hill and this sequence may be repeated at regular intervals along the length of the ion guide 3 so as to create a repeating pattern of potential wells separated by potential hills. The potential wells may according to less preferred embodiments be spaced at non-regular intervals. The height of the potential hills is preferably sufficient to trap ions positioned between neighbouring potential hills so that ions are preferably trapped and stored in the different potential wells along the length of the ion guide 3 according to their mass to charge ratios. Ions may oscillate within each potential well but, if required, may be subsequently dampened by the introduction of a gas into the ion guide 3 which has the effect of damping the ion motion. The presence of gas will also result in collisions between the ions and gas molecules and ions will lose energy through such collisions with gas molecules until their energies are reduced to that of the background gas. As the ions lose energy they tend to occupy the lowest positions within the potential wells. The ions are preferably stored in the potential wells until released for subsequent analysis.

Fig. 2 illustrates how ions having different mass to charge ratios may be distributed along the ion

- 5 -

guide/ion trap 3 when trapping potentials are applied so as to collect and store ions in different potential wells. In this particular example the length L1 of the upstream ion guide 2 is 150 mm and the length L2 of the segmented ion guide ion trap 3 is also 150 mm. The segmented ion guide 3 is arranged to contain ten potential wells spaced at regular intervals of 15 mm e.g. 15, 30, 45, 60, 75, 90, 105, 120 and 135 mm. The ion energy is 3 eV and the trapping potentials along the segmented ion guide 3 were applied 315 μ s after a pulse of ions was accelerated from the ion source 1. In this illustration the ions collected in the first potential well have mass to charge ratios in the range 2100-2550 and ions collected in the last potential well have mass to charge ratios in the range 700-800.

According to a second main embodiment the ions may arrive at the RF ion guide 3 on which a travelling DC potential wave has been superimposed. As the ions arrive at the entrance to the RF ion guide 3 they will coincide with the appearance of a potential well travelling in the same direction as the ions. These ions will travel with this potential well. Ions with slightly higher mass to charge ratios will arrive at progressively later times and will also travel with this potential well. However after a short period of time a new potential hill will emerge, which will also be travelling in the same direction as the ions. Ions arriving after the new potential hill has emerged will therefore be too late to be collected within the preceding potential well and hence will now therefore be collected and travel within the newly emerged potential well. As will be appreciated, further potential wells will be created as ions continue to arrive at the ion

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guide ion trap 3. Hence each potential well will collect a series of ions with a range of mass to charge ratios higher than the previous potential well. Ions may oscillate within each potential well but if required
5 may be subsequently dampened by the introduction of a gas into the ion trap 3 to dampen ion motion.

The width of the potential wells which are created along the ion guide 3 may be varied so that the range of mass to charge ratios that are collected in each well
10 can be determined at will. Fig. 3 shows how the collection of ions might be distributed according to their mass to charge ratios in such a device where the travelling wave has a constant velocity and a constant wavelength. In this example the lengths L1 and L2 of
15 the first and second ion guides 2, 3 are both 150 mm. The travelling wave has a wavelength of 15 mm and wave cycle time of 30 μ s. The ion energy is 1 eV and the Figure shows the range of mass to charge ratios collected in each potential well over the period from
20 300 μ s to 600 μ s from the release of ions from the ion source 1. Ions collected in the first well (after 300 μ s) have mass to charge ratios in the range 780 to 920. Ions collected in the last well (up to 600 μ s) have mass to charge ratios in the range 2500 to 2790. In the
25 example shown further potential wells are generated after 330, 360, 420, 450, 480, 510, 540 and 570 μ s.

According to the second main embodiment the velocity of the travelling wave progressively slows down to match the velocity of the ions arriving at the RF ion
30 guide 3. For example, if the ions from the ion source 1 are accelerated to a given energy and are allowed to pass through a field free region 2 at relatively low pressure then ions of different masses will travel at

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different velocities. Ions with lower mass to charge ratios will have higher velocities and will arrive at the travelling wave device 3 before ions with higher mass to charge ratios that have lower velocities. On arrival at the travelling wave ion guide 3 ions will be collected in groups according to their mass to charge ratio and will be transported through the travelling wave device 3 as a discrete group. The velocity of the travelling wave preferably substantially matches that of the arriving ions and hence its velocity should decrease as ions with progressively higher mass to charge ratios arrive at the ion guide 3. Likewise the velocity of the ions already collected in the travelling potential wells should also decrease to match that of the travelling wave. Ion motion may be dampened by the presence or introduction of a buffer gas. Under the right conditions the ion velocity may be made to decrease at the same rate as that of the travelling wave.

In the following analysis it is assumed that ions are released from a pulsed ion source 1, for example a laser ablation or MALDI ion source, or from an ion trap. Ions then travel through an RF ion guide 2 with zero axial electric field and then enter an RF ion guide 3 with superimposed travelling wave. The ion guide 2 with zero axial electric field is preferably at a relatively low pressure (e.g. less than 0.0001 mbar) and the travelling wave ion guide 3 is preferably at intermediate pressure (e.g. between 0.001 and 1 mbar).

In the following the distance in meters from the pulsed ion source 1 or ion trap to the entrance of the travelling wave ion guide (i.e. the length of the drift region 2) is L_1 , the length of the travelling wave ion guide 3 is L_2 and the distance from the exit of the

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travelling wave ion guide 3 to the centre of an
orthogonal acceleration Time of Flight acceleration
region is L_3 . The ions are preferably accelerated
through a voltage difference of V_1 at the ion source or
5 ion trap so that they have energy E_1 of zeV_1 electron
volts. Accordingly, for ions having a mass to charge
ratio m/z the arrival time T_1 (in μs) of ions at the
entrance to the travelling wave ion guide 3 after they
have been ejected from the ion source 1 or emitted from
10 an upstream ion trap is given by:

$$T_1 = 72 L_1 \sqrt{\frac{m}{zeV_1}}$$

The velocity v of these ions will be:

15
$$v = \frac{L_1}{T_1}$$

The travelling wave ion guide 3 is preferably
maintained at a pressure between 0.0001 and 100 mbar,
further preferably between 0.001 and 10 mbar. At these
20 pressures the gas density is sufficient to impose a
viscous drag on the ions and hence the gas will appear
as a viscous medium to the ions and will act to slow the
ions.

It is preferably arranged that the velocity v_{wave} of
25 the travelling wave is equal to the velocity v of the
ions as they arrive at the entrance to the travelling
wave ion guide 3. Since the velocity of the ions
arriving at the entrance to the ion guide 3 is inversely
proportional to elapsed time T_1 from release of ions
30 from the ion source 1 or ion trap then the velocity v_{wave}

- 9 -

of the travelling wave also preferably decreases with time in the same way.

Since the wave velocity v_{wave} is equal to λ/T where λ is the wavelength and T is the cycle time of the waveform, then it follows that the cycle time T should vary in proportion to the elapsed time T_1 . In other words, for the wave velocity to always equal the velocity of the ions arriving at the entrance to the preferred ion guide the wave cycle time T should preferably increase linearly with time.

Since the wave velocity v_{wave} preferably continuously slows it may be expected that the ions would travel on ahead of the wave. However, the viscous drag resulting from frequent collisions with gas molecules tends to prevent the ions from building up excessive velocity. Consequently the ions will tend to ride on the travelling wave rather than run ahead of the wave and execute excessive oscillations within the travelling potential wells.

If, in time δt , the ions travel distance δl within the ion guide 3:

$$\delta l = v \delta t$$

then if the time at which the ions exit the travelling wave ion guide 3 is T_2 then the distance ΔL travelled within the ion guide is:

$$\Delta L = \int_{T_1}^{T_2} v \delta t$$

30

$$\Delta L = \int_{T_1}^{T_2} \frac{L_1}{t} \delta t$$

- 10 -

$$\Delta L = L_1 (\ln(T_2) - \ln(T_1))$$

$$\Delta L = L_1 \ln\left(\frac{T_2}{T_1}\right)$$

5

Since the length of the ion guide 3 is L_2 and hence $\Delta L = L_2$ then:

$$L_2 = L_1 \ln\left(\frac{T_2}{T_1}\right)$$

10

$$T_2 = T_1 e^{\left(\frac{L_2}{L_1}\right)}$$

15

Hence, the velocity of the ions v_x as they exit the travelling wave ion guide 3 is equal to that of the travelling wave at the time of exit and therefore is:

$$v_x = \frac{L_1}{T_2}$$

$$v_x = \frac{L_1}{T_1} e^{-\left(\frac{L_2}{L_1}\right)}$$

20

$$v_x = v e^{-\left(\frac{L_2}{L_1}\right)}$$

25

Since the energy E_1 of the ions at the entrance to the ion guide 3 is:

$$E_1 = zeV_1$$

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then since:

$$E = \frac{1}{2}mv^2$$

5

if the energy of the ions at the exit of the ion guide 3 is E_2 then:

$$E_2 = \frac{1}{2}mv_x^2$$

10

$$E_2 = \frac{1}{2}mv^2 e^{-2\left(\frac{L_2}{L_1}\right)}$$

$$E_2 = E_1 e^{-2\left(\frac{L_2}{L_1}\right)}$$

15

Hence for such an arrangement where the wave velocity is matched to that of the arriving ions it follows that for ions within the travelling wave ion guide 3 their velocity and energy preferably decay exponentially with the distance travelled into the ion guide 3.

20

The gas in the travelling wave ion guide 3 preferably causes frequent ion-molecule collisions which in turn will cause the ions to lose kinetic energy. In the presence of an RF confining field both the axial and radial kinetic energies will therefore be reduced.

Furthermore, the axial and radial energies decay approximately exponentially with distance travelled into the ion guide (J. Am. Soc. Mass Spectrom., 1998, 9, pp 569-579). From computer simulations it is estimated

25

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that the kinetic energies in axial and radial directions reduce to 10% whilst passing through a nitrogen gas pressure-distance product of approximately 0.1 mbar-cm. Hence, both the wave velocity and the ion kinetic energies will decay exponentially. The exponential decay rate of the wave velocity can therefore preferably be set so as to substantially match the natural decay of the ion kinetic energy. If the wave velocity is significantly greater than the natural decay rate of the ion kinetic energy then the ions may be caused to fragment whilst passing through the ion guide 3.

As the ions enter the travelling wave ion guide 3 then according to one embodiment they will be grouped such that each group contains only ions within a limited range of mass to charge ratios and each group will have ions with mass to charge ratios higher than those of the preceding group which arrived within the ion guide 3. After the last ions of interest have entered the ion guide 3 the travelling wave can be halted and the ions will remain trapped in their respective potential wells according to their mass to charge ratios. Any further damping of ion motion that may be required will take place for as long as the buffer gas pressure in the device 3 is maintained. Ions may now be stored and released for subsequent analysis when required.

Ions may be released from the series of potential wells either from the end to which they were travelling or from the end through which they entered the ion guide 3. In the former case the ions will be released in increasing order of mass to charge ratio value starting with those with the lowest mass to charge ratios stored. In the latter case ions are reversed in direction to be released from the end of the ion guide 3 through which

- 13 -

they entered. In this case ions will be released in decreasing order of mass to charge ratio starting with those with the highest mass to charge ratios stored. Ions may be released by lowering the potential hill or barrier retaining the ions and accelerating the ions out in the required direction. Alternatively, ions may be released by moving the waveform along one wavelength in the required direction. This will push out the ions in the group nearest the exit and at the same time move all the other ions in their respective groups one wavelength nearer to the exit.

The preferred ion guide 3 provides a means of efficiently allowing a large number of components from a mixture of components to be analysed in a tandem mass spectrometer by means of collision induced fragmentation and subsequent mass analysis of the fragment ions. The ion guide 3 allows the components to be separated, or partially separated, into groups according to their mass to charge ratios, stored in a series of separate potential wells and subsequently analysed in groups, one group at a time. Furthermore, if required, ions of one mass to charge ratio from each group may be first selected before fragmentation and mass analysis.

According to an embodiment the ion source 1 may comprise a pulsed ion source, such as a Matrix Assisted Laser Desorption Ionisation ion source (MALDI). A pulse of ions emitted from the ion source 1 may be collected and cooled in an RF ion trapping device 2. This could be a segmented RF ion guide that also functions as an ion trap by virtue of being able to be programmed with different DC potentials along its length. When used to trap ions it may be programmed to have an axial potential well at some point along its length. It may

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be a segmented multi-pole rod set, or a stacked ring set, or a stacked plate set in the form of a sandwich, or some combination of these devices. It is not necessary for this device to be a mass selective ion trap such as a quadrupole ion trap. The device for trapping ions may use a buffer gas for cooling the ions. This may help to improve the trapping efficiency of this device and also cools energetic ions from the ion source.

5 If it is only required to mass analyse the trapped ions the ions may now be released downstream to an ion guide and subsequent mass analyser. The mass analyser may comprise a quadrupole mass filter, a linear or 3-D quadrupole ion trap, a Time of Flight mass analyser, an FT ICR mass analyser, or a magnetic sector mass analyser. Preferably, the mass analyser is an orthogonal acceleration Time of Flight mass analyser.

10 If on the other hand it is required to fragment and analyse a number of different ions from the mixture of ions released from the ion source 1 and collected in the ion trapping device the ions may then be released from the ion trapping device in a single pulse in the direction of a quadrupole ion guide and further ion collection and storage device which may be provided upstream of the ion trapping device 3. The quadrupole RF ion guide allows ions to be separated according to their mass to charge ratios and the further ion collection and storage device allows ions to be collected and stored in groups according to their mass to charge ratios as already described. Preferably the further ion collection and storage device is provided with a progressively slowing travelling wave as described above. Ions may now be released from the

- 15 -

~~series of potential wells~~ in the further ion storage device in reverse order starting with ions with the highest mass to charge ratios. Ions from the first group are then preferably ejected in the reverse direction back through the quadrupole RF ion guide and into the ion trapping device. The quadrupole RF ion guide may be operated in the non-resolving (RF only) mode such as to transmit all the ions within that group. Alternatively, the quadrupole ion guide may be operated in the resolving (RF and DC) mode such as to transmit ions with just one, or with a limited range, of mass to charge ratios. In the ion trapping device the ions may be fragmented by collision activation with the buffer gas. The fragment ions may then preferably be trapped in the ion trapping device. The fragment ions may then be released in the direction of the ion guide and the mass analyser arranged downstream of the ion trapping device.

This procedure may be repeated for the next group of ions from the next potential well in the further ion collection and storage device. This may be repeated again and again until all the groups of ions have been analysed, or ions of selected mass to charge ratio within each group have been analysed. Hence, the further ion collection and storage device behaves as a fraction collection device for ions with different mass to charge ratios and allows many different fragmentation and mass analyses to be performed from the original mixture of ions.

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Claims

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1. A mass spectrometer comprising:

an ion trap comprising a plurality of electrodes wherein at a first time t_1 ions enter said ion trap and wherein at a second later time t_2 a plurality of axial trapping regions are formed or created along the length of said ion trap.

10

2. A mass spectrometer as claimed in claim 1, wherein at said first time t_1 no axial trapping regions other than at an entrance or exit of said ion trap are provided along said ion trap.

15

3. A mass spectrometer as claimed in claim 1 or 2, wherein said ion trap has an entrance for receiving ions and an exit from which ions exit in use and wherein at said second time t_2 ions have travelled from said entrance at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% of the axial length of said ion trap towards said exit.

20

25

4. A mass spectrometer as claimed in any preceding claim, wherein the difference between t_2 and t_1 is selected from the group consisting of: (i) 1-100 μ s; (ii) 100-200 μ s; (iii) 200-300 μ s; (iv) 300-400 μ s; (v) 400-500 μ s; (vi) 500-600 μ s; (vii) 600-700 μ s; (viii) 700-800 μ s; (ix) 800-900 μ s; (x) 900-1000 μ s.

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5. A mass spectrometer as claimed in any preceding claim, wherein the difference between t_2 and t_1 is selected from the group consisting of: (i) 1-2 ms; (ii) 2-3 ms; (iii) 3-4 ms; (iv) 4-5 ms; (v) 5-6 ms; (vi) 6-7 ms; (viii) 7-8 ms; (ix) 8-9 ms; (x) 9-10 ms; (xi) 10-11 ms; (xii) 11-12 ms; (xiii) 12-13 ms; (xiv) 13-14 ms; (xv) 14-15 ms; (xvi) 15-16 ms; (xvii) 16-17 ms; (xviii) 17-18 ms; (xix) 18-19 ms; (xx) 19-20 ms; (xxi) 20-21 ms; (xxii) 21-22 ms; (xxiii) 22-23 ms; (xxiv) 23-24 ms; (xxv) 24-25 ms; (xxvi) 25-26 ms; (xxvii) 26-27 ms; (xxviii) 27-28 ms; (xxix) 28-29 ms; (xxx) 29-30 ms; or (xxxi) > 30 ms.

6. A mass spectrometer comprising:
an ion trap comprising a plurality of electrodes, wherein in use ions received within said ion trap are trapped in one or more axial trapping regions within said ion trap and wherein said one or more axial trapping regions are translated along at least a portion of the axial length of said ion trap with an initial first velocity and wherein said first velocity is progressively reduced to a velocity less than 5 m/s.

7. A mass spectrometer as claimed in claim 6, wherein said first velocity is progressively reduced to a velocity selected from the group consisting of: (i) < 4 m/s; (ii) < 3 m/s; (iii) < 2 m/s; (iv) < 1 m/s; and (v) substantially zero.

8. A mass spectrometer comprising:
an ion trap comprising a plurality of electrodes, wherein in use ions received within said ion trap are trapped in one or more axial trapping regions within

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~~said ion trap~~ and wherein ~~said one or more axial~~
trapping regions are translated along at least a portion
of the axial length of said ion trap with an initial
first velocity and wherein said first velocity is
5 progressively reduced to zero.

9. A mass spectrometer as claimed in any preceding
claim, further comprising a device for temporally or
spatially dispersing a group of ions according to a
10 physico-chemical property, said device being arranged
upstream of said ion trap.

10. A mass spectrometer as claimed in claim 9; wherein
said physico-chemical property is mass to charge ratio.

15 11. A mass spectrometer as claimed in claim 10, further
comprising a field free region arranged upstream of said
ion trap wherein ions which have been accelerated to
have substantially the same kinetic energy become
20 dispersed according to their mass to charge ratio.

12. A mass spectrometer as claimed in claim 11, wherein
said field free region is provided within an ion guide.

25 13. A mass spectrometer as claimed in claim 12, wherein
said ion guide is selected from the group consisting of:
(i) a quadrupole rod set; (ii) a hexapole rod set; (iii)
an octopole or higher order rod set; (iv) an ion tunnel
ion guide comprising a plurality of electrodes having
30 apertures through which ions are transmitted, said
apertures being substantially the same size; (v) an ion
funnel ion guide comprising a plurality of electrodes
having apertures through which ions are transmitted,

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said apertures becoming progressively smaller or larger;
and (vi) a segmented rod set.

14. A mass spectrometer as claimed in any of claims 11,
5 12 or 13, further comprising a pulsed ion source wherein
in use a packet of ions emitted by said pulsed ion
source enters said field free region.

15. A mass spectrometer as claimed in any of claims 11-
10 14, further comprising an ion trap arranged upstream of
the field free region wherein in use said ion trap
releases a packet of ions which enters said field free
region.

16. A mass spectrometer as claimed in claim 9, wherein
15 said physico-chemical property is ion mobility.

17. A mass spectrometer as claimed in claim 16, further
comprising a drift region arranged upstream of said ion
20 trap wherein ions become dispersed according to their
mobility.

18. A mass spectrometer as claimed in claim 17, wherein
said drift region is provided within an ion guide.

25

19. A mass spectrometer as claimed in claim 18, wherein
said ion guide is selected from the group consisting of:
(i) a quadrupole rod set; (ii) a hexapole rod set; (iii)
an octopole or higher order rod set; (iv) an ion tunnel
30 ion guide comprising a plurality of electrodes having
apertures through which ions are transmitted, said
apertures being substantially the same size; (v) an ion
funnel ion guide comprising a plurality of electrodes

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having apertures through which ions are transmitted, said apertures becoming progressively smaller or larger; and (vi) a segmented rod set.

- 5 20. A mass spectrometer as claimed in any of claims 16-19, further comprising a pulsed ion source wherein in use a packet of ions emitted by said pulsed ion source enters said drift region.
- 10 21. A mass spectrometer as claimed in any of claims 16-20, further comprising an ion trap arranged upstream of the drift region wherein in use said ion trap releases a packet of ions which enters said drift region.
- 15 22. A mass spectrometer as claimed in any preceding claim, wherein said ion trap has an entrance for receiving ions and an exit disposed at the other end of said ion trap to said entrance and wherein at a point in time said one or more axial trapping regions are
- 20 translated towards said entrance.
23. A mass spectrometer as claimed in any preceding claims, wherein said ion trap has an entrance for receiving ions and an exit disposed at the other end of
- 25 said ion trap to said entrance and wherein at a point in time said one or more axial trapping regions are translated towards said exit.
24. A mass spectrometer as claimed in any preceding
- 30 claim, wherein a potential barrier between two or more trapping regions is removed so that said two or more trapping regions form a single trapping region or

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lowered so that ~~at least some ions are able to be move~~
between said two or more trapping regions.

25. A mass spectrometer as claimed in any preceding
5 claim, wherein, in use, one or more transient DC
voltages or one or more transient DC voltage waveforms
are progressively applied to said electrodes so that
ions are urged along said ion trap.

10 26. A mass spectrometer as claimed in any preceding
claim, wherein in use an axial voltage gradient is
maintained along at least a portion of the length of
said ion trap and wherein said axial voltage gradient
varies with time.

15 27. A mass spectrometer as claimed in any preceding
claim, wherein said ion trap comprises a first electrode
held at a first reference potential, a second electrode
held at a second reference potential, and a third
20 electrode held at a third reference potential, wherein:
at a first time t_1 a first DC voltage is supplied
to said first electrode so that said first electrode is
held at a first potential above or below said first
reference potential;

25 at a second later time t_2 a second DC voltage is
supplied to said second electrode so that said second
electrode is held at a second potential above or below
said second reference potential; and

30 at a third later time t_3 a third DC voltage is
supplied to said third electrode so that said third
electrode is held at a third potential above or below
said third reference potential.

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28. A mass spectrometer as claimed in claim 27,
wherein:

5 at said first time t_1 said second electrode is at
said second reference potential and said third electrode
is at said third reference potential;

at said second time t_2 said first electrode is at
said first potential and said third electrode is at said
third reference potential; and

10 at said third time t_3 said first electrode is at
said first potential and said second electrode is at
said second potential.

29. A mass spectrometer as claimed in claim 27,
wherein:

15 at said first time t_1 said second electrode is at
said second reference potential and said third electrode
is at said third reference potential;

20 at said second time t_2 said first electrode is no
longer supplied with said first DC voltage so that said
first electrode is returned to said first reference
potential and said third electrode is at said third
reference potential; and

25 at said third time t_3 said second electrode is no
longer supplied with said second DC voltage so that said
second electrode is returned to said second reference
potential and said first electrode is at said first
reference potential.

30 30. A mass spectrometer as claimed in any of claims 27-
29, wherein said first, second and third reference
potentials are substantially the same and/or said first,
second and third DC voltages are substantially the same

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and/or said first, second and third potentials are substantially the same.

31. A mass spectrometer as claimed in any preceding
5 claim, wherein said ion trap comprises 3, 4, 5, 6, 7, 8,
9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22,
23, 24, 25, 26, 27, 28, 29, 30 or >30 segments, wherein
each segment comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10,
11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24,
10 25, 26, 27, 28, 29, 30 or >30 electrodes electrically
connected together.

32. A mass spectrometer as claimed in claim 31 wherein
a plurality of segments are electrically connected
15 together.

33. A mass spectrometer as claimed in claim 32, wherein
each segment is electrically connected to the nth
subsequent segment wherein n is selected from 4, 5, 6,
20 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21,
22, 23, 24, 25, 26, 27, 28, 29, 30 or >30.

34. A mass spectrometer as claimed in any preceding
claim, wherein ions are: (ii) confined radially within
25 said ion trap by an AC or RF electric field; (ii)
radially confined within said ion trap in a pseudo-
potential well and are constrained axially by a real
potential barrier or well.

30 35. A mass spectrometer as claimed in any preceding
claim, wherein the transit time of ions through said ion
trap is selected from the group consisting of: (i) less
than or equal to 20 ms; (ii) less than or equal to 10

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ms; (iii) less than or equal to 5 ms; (iv) less than or equal to 1 ms; and (v) less than or equal to 0.5 ms.

36. A mass spectrometer as claimed in any preceding
5 claim, wherein said ion trap and/or said drift region is
maintained, in use, at a pressure selected from the
group consisting of: (i) greater than or equal to 0.0001
mbar; (ii) greater than or equal to 0.0005 mbar; (iii)
greater than or equal to 0.001 mbar; (iv) greater than
10 or equal to 0.005 mbar; (v) greater than or equal to
0.01 mbar; (vi) greater than or equal to 0.05 mbar;
(vii) greater than or equal to 0.1 mbar; (viii) greater
than or equal to 0.5 mbar; (ix) greater than or equal to
1 mbar; (x) greater than or equal to 5 mbar; and (xi)
15 greater than or equal to 10 mbar.

37. A mass spectrometer as claimed in any preceding
claim, wherein said ion trap and/or said drift region is
maintained, in use, at a pressure selected from the
20 group consisting of: (i) less than or equal to 10 mbar;
(ii) less than or equal to 5 mbar; (iii) less than or
equal to 1 mbar; (iv) less than or equal to 0.5 mbar;
(v) less than or equal to 0.1 mbar; (vi) less than or
equal to 0.05 mbar; (vii) less than or equal to 0.01
25 mbar; (viii) less than or equal to 0.005 mbar; (ix) less
than or equal to 0.001 mbar; (x) less than or equal to
0.0005 mbar; and (xi) less than or equal to 0.0001 mbar.

38. A mass spectrometer as claimed in any preceding
30 claim, wherein said ion trap and/or said drift region is
maintained, in use, at a pressure selected from the
group consisting of: (i) between 0.0001 and 10 mbar;
(ii) between 0.0001 and 1 mbar; (iii) between 0.0001 and

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0.1 mbar; (iv) between 0.0001 and 0.01 mbar; (v) between 0.0001 and 0.001 mbar; (vi) between 0.001 and 10 mbar; (vii) between 0.001 and 1 mbar; (viii) between 0.001 and 0.1 mbar; (ix) between 0.001 and 0.01 mbar; (x) between 0.01 and 10 mbar; (xi) between 0.01 and 1 mbar; (xii) between 0.01 and 0.1 mbar; (xiii) between 0.1 and 10 mbar; (xiv) between 0.1 and 1 mbar; (xv) between 1 and 10 mbar; and (xvi) above 10 mbar.

39. A mass spectrometer as claimed in any preceding claim, wherein said ion trap and/or said drift region is maintained, in use, at a pressure such that a viscous drag is imposed upon ions passing through said ion trap.

40. A mass spectrometer as claimed in any of claims 11-15, wherein said field free region is maintained, in use, at a pressure selected from the group consisting of: (i) greater than or equal to 1×10^{-7} mbar; (ii) greater than or equal to 5×10^{-7} mbar; (iii) greater than or equal to 1×10^{-6} mbar; (iv) greater than or equal to 5×10^{-6} mbar; (v) greater than or equal to 1×10^{-5} mbar; and (vi) greater than or equal to 5×10^{-5} mbar.

41. A mass spectrometer as claimed in any of claims 11-15 or 40, wherein said field free region is maintained, in use, at a pressure selected from the group consisting of: (i) less than or equal to 1×10^{-4} mbar; (ii) less than or equal to 5×10^{-5} mbar; (iii) less than or equal to 1×10^{-5} mbar; (iv) less than or equal to 5×10^{-6} mbar; (v) less than or equal to 1×10^{-6} mbar; (vi) less than or equal to 5×10^{-7} mbar; and (vii) less than or equal to 1×10^{-7} mbar.

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42. A mass spectrometer as claimed in any of ~~claims~~ 11-15, 40 or 41, wherein said field free region is maintained, in use, at a pressure selected from the group consisting of: (i) between 1×10^{-7} and 1×10^{-4} mbar; (ii) between 1×10^{-7} and 5×10^{-5} mbar; (iii) between 1×10^{-7} and 1×10^{-5} mbar; (iv) between 1×10^{-7} and 5×10^{-6} mbar; (v) between 1×10^{-7} and 1×10^{-6} mbar; (vi) between 1×10^{-7} and 5×10^{-7} mbar; (vii) between 5×10^{-7} and 1×10^{-4} mbar; (viii) between 5×10^{-7} and 5×10^{-5} mbar; (ix) between 5×10^{-7} and 1×10^{-5} mbar; (x) between 5×10^{-7} and 5×10^{-6} mbar; (xi) between 5×10^{-7} and 1×10^{-6} mbar; (xii) between 1×10^{-6} mbar and 1×10^{-4} mbar; (xiii) between 1×10^{-6} and 5×10^{-5} mbar; (xiv) between 1×10^{-6} and 1×10^{-5} mbar; (xv) between 1×10^{-6} and 5×10^{-6} mbar; (xvi) between 5×10^{-6} mbar and 1×10^{-4} mbar; (xvii) between 5×10^{-6} and 5×10^{-5} mbar; (xviii) between 5×10^{-6} and 1×10^{-5} mbar; (xix) between 1×10^{-5} mbar and 1×10^{-4} mbar; (xx) between 1×10^{-5} and 5×10^{-5} mbar; (xxi) between 5×10^{-5} and 1×10^{-4} mbar.

43. A mass spectrometer as claimed in any preceding claim, wherein in use one or more transient DC voltages or one or more transient DC voltage waveforms are provided at a first axial position and are then subsequently provided at second, then third different axial positions along said ion trap.

44. A mass spectrometer as claimed in any preceding claim, wherein in use one or more transient DC voltages or one or more transient DC voltage waveforms are arranged to move from one end of said ion trap to another end of said ion trap so that ions are urged along said ion trap.

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45. A mass spectrometer as claimed in claim 43 or 44, wherein said one of more transient DC voltages create:
(i) a potential hill or barrier; (ii) a potential well;
(iii) multiple potential hills or barriers; (iv)
5 multiple potential wells; (v) a combination of a potential hill or barrier and a potential well; or (vi) a combination of multiple potential hills or barriers and multiple potential wells.
- 10 46. A mass spectrometer as claimed in claim 43 or 44, wherein said one or more transient DC voltage waveforms comprise a repeating waveform.
- 15 47. A mass spectrometer as claimed in claim 46, wherein said one or more transient DC voltage waveforms comprise a square wave.
- 20 48. A mass spectrometer as claimed in any of claims 43-47, wherein either: (i) the amplitude of said one or more transient DC voltages or said one or more transient DC voltage waveforms remains substantially constant with time; or (ii) the amplitude of said one or more transient DC voltages or said one or more transient DC voltage waveforms varies with time.
- 25 49. A mass spectrometer as claimed in any of claims 43-47, wherein the amplitude of said one or more transient DC voltages or said one or more transient DC voltage waveforms either: (i) increases with time; (ii)
30 increases then decreases with time; (iii) decreases with time; or (iv) decreases then increases with time.

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50. A mass spectrometer as claimed in any of claims 43-49, wherein said ion trap comprises an upstream entrance region, a downstream exit region and an intermediate region, wherein:

5 in said entrance region the amplitude of said one or more transient DC voltages or one or more transient DC voltage waveforms has a first amplitude;

in said intermediate region the amplitude of said one or more transient DC voltages or one or more transient DC voltage waveforms has a second amplitude; and

in said exit region the amplitude of said one or more transient DC voltages or one or more transient DC voltage waveforms has a third amplitude.

15

51. A mass spectrometer as claimed in claim 50, wherein the entrance and/or exit region comprise a proportion of the total axial length of said ion trap selected from the group consisting of: (i) < 5%; (ii) 5-10%; (iii) 10-15%; (iv) 15-20%; (v) 20-25%; (vi) 25-30%; (vii) 30-35%; (viii) 35-40%; and (ix) 40-45%.

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52. A mass spectrometer as claimed in claim 50 or 51, wherein said first and/or third amplitudes are substantially zero and said second amplitude is substantially non-zero.

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53. A mass spectrometer as claimed in claim 50, 51 or 52, wherein said second amplitude is larger than said first amplitude and/or said second amplitude is larger than said third amplitude.

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54. A mass spectrometer as claimed in any preceding claim, wherein said one or more axial trapping regions are translated along said ion trap with a first velocity and cause ions within said ion trap to pass along said ion trap with a second velocity.

55. A mass spectrometer as claimed in claim 54, wherein the difference between said first velocity and said second velocity is selected from the group consisting of: (i) less than or equal to 50 m/s; (ii) less than or equal to 40 m/s; (iii) less than or equal to 30 m/s; (iv) less than or equal to 20 m/s; (v) less than or equal to 10 m/s; (vi) less than or equal to 5 m/s; and (vii) less than or equal to 1 m/s;

15

56. A mass spectrometer as claimed in any claim 54 or 55, wherein said first velocity is selected from the group consisting of: (i) 10-250 m/s; (ii) 250-500 m/s; (iii) 500-750 m/s; (iv) 750-1000 m/s; (v) 1000-1250 m/s; (vi) 1250-1500 m/s; (vii) 1500-1750 m/s; (viii) 1750-2000 m/s; (ix) 2000-2250 m/s; (x) 2250-2500 m/s; (xi) 2500-2750 m/s; (xii) 2750-3000 m/s; (xiii) 3000-3250 m/s; (xiv) 3250-3500 m/s; (xv) 3500-3750 m/s; (xvi) 3750-4000 m/s; (xvii) 4000-4250 m/s; (xviii) 4250-4500 m/s; (xix) 4500-4750 m/s; (xx) 4750-5000 m/s; and (xxi) > 5000 m/s.

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25

57. A mass spectrometer as claimed in claim 54, 55 or 56, wherein said second velocity is selected from the group consisting of: (i) 10-250 m/s; (ii) 250-500 m/s; (iii) 500-750 m/s; (iv) 750-1000 m/s; (v) 1000-1250 m/s; (vi) 1250-1500 m/s; (vii) 1500-1750 m/s; (viii) 1750-2000 m/s; (ix) 2000-2250 m/s; (x) 2250-2500 m/s; (xi)

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2500-2750 m/s; (xii) 2750-3000 m/s; (xiii) 3000-3250 m/s; (xiv) 3250-3500 m/s; (xv) 3500-3750 m/s; (xvi) 3750-4000 m/s; (xvii) 4000-4250 m/s; (xviii) 4250-4500 m/s; (xix) 4500-4750 m/s; (xx) 4750-5000 m/s; and (xxi) > 5000 m/s.

58. A mass spectrometer as claimed in any of claims 54-57, wherein said second velocity is substantially the same as said first velocity.

10

59. A mass spectrometer as claimed in any of claims 43-58, wherein said one or more transient DC voltages or said one or more transient DC voltage waveforms passed along said ion trap has a frequency, and wherein said frequency: (i) remains substantially constant; (ii) varies; (iii) increases; (iv) increases then decreases; (v) decreases; or (vi) decreases then increases.

15

60. A mass spectrometer as claimed in any of claims 43-59, wherein said one or more transient DC voltages or said one or more transient DC voltage waveforms passed along said ion trap has a wavelength, and wherein said wavelength: (i) remains substantially constant; (ii) varies; (iii) increases; (iv) increases then decreases; (v) decreases; or (vi) decreases then increases.

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25

61. A mass spectrometer as claimed in any preceding claim, wherein two or more transient DC voltages or two or more transient DC voltage waveforms are arranged to be passed simultaneously along said ion trap.

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62. A mass spectrometer as claimed in claim 61, wherein said two or more transient DC voltages or said two or

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more transient DC voltage waveforms are arranged to move: (i) in the same direction; (ii) in opposite directions; (iii) towards each other; (iv) away from each other.

5

63. A mass spectrometer as claimed in any of claims 43-62, wherein said one or more transient DC voltages or said one or more transient DC voltage waveforms are repeatedly generated and passed in use along said ion trap, and wherein the frequency of generating said one or more transient DC voltages or said one or more transient DC voltage waveforms: (i) remains substantially constant; (ii) varies; (iii) increases; (iv) increases then decreases; (v) decreases; or (vi) decreases then increases.

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15

64. A mass spectrometer as claimed in any preceding claim, further comprising a Time of Flight mass analyser comprising an electrode for injecting ions into a drift region, said electrode being arranged to be energised in use in a substantially synchronised manner with a pulse of ions emitted from the exit of said ion trap.

20

65. A mass spectrometer as claimed in any preceding claim, wherein said ion trap is selected from the group consisting of: (i) an ion funnel comprising a plurality of electrodes having apertures therein through which ions are transmitted, wherein the diameter of said apertures becomes progressively smaller or larger; (ii) an ion tunnel comprising a plurality of electrodes having apertures therein through which ions are transmitted, wherein the diameter of said apertures

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remains substantially constant; and (iii) a stack of plate, ring or wire loop electrodes.

5 66. A mass spectrometer as claimed in any preceding claim, wherein said ion trap comprises a plurality of electrodes, each electrode having an aperture through which ions are transmitted in use.

10 67. A mass spectrometer as claimed in any preceding claim, wherein each electrode has a substantially circular aperture.

15 68. A mass spectrometer as claimed in any preceding claim, wherein each electrode has a single aperture through which ions are transmitted in use.

20 69. A mass spectrometer as claimed in claim 66, 67 or 68, wherein the diameter of the apertures of at least 50%, 60%, 70%, 80%, 90% or 95% of the electrodes forming said ion trap is selected from the group consisting of:
(i) less than or equal to 10 mm; (ii) less than or equal to 9 mm; (iii) less than or equal to 8 mm; (iv) less than or equal to 7 mm; (v) less than or equal to 6 mm; (vi) less than or equal to 5 mm; (vii) less than or
25 equal to 4 mm; (viii) less than or equal to 3 mm; (ix) less than or equal to 2 mm; and (x) less than or equal to 1 mm.

30 70. A mass spectrometer as claimed in any preceding claim, wherein at least 50%, 60%, 70%, 80%, 90% or 95% of the electrodes forming the ion trap have apertures which are substantially the same size or area.

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71. A mass spectrometer as claimed in any of claims 1-64, wherein said ion trap comprises a segmented rod set.

72. A mass spectrometer as claimed in any preceding claim, wherein said ion trap consists of: (i) 10-20 electrodes; (ii) 20-30 electrodes; (iii) 30-40 electrodes; (iv) 40-50 electrodes; (v) 50-60 electrodes; (vi) 60-70 electrodes; (vii) 70-80 electrodes; (viii) 80-90 electrodes; (ix) 90-100 electrodes; (x) 100-110 electrodes; (xi) 110-120 electrodes; (xii) 120-130 electrodes; (xiii) 130-140 electrodes; (xiv) 140-150 electrodes; or (xv) more than 150 electrodes.

73. A mass spectrometer as claimed in any preceding claim, wherein the thickness of at least 50%, 60%, 70%, 80%, 90% or 95% of said electrodes is selected from the group consisting of: (i) less than or equal to 3 mm; (ii) less than or equal to 2.5 mm; (iii) less than or equal to 2.0 mm; (iv) less than or equal to 1.5 mm; (v) less than or equal to 1.0 mm; and (vi) less than or equal to 0.5 mm.

74. A mass spectrometer as claimed in any preceding claim, wherein said ion trap has a length selected from the group consisting of: (i) less than 5 cm; (ii) 5-10 cm; (iii) 10-15 cm; (iv) 15-20 cm; (v) 20-25 cm; (vi) 25-30 cm; and (vii) greater than 30 cm.

75. A mass spectrometer as claimed in any preceding claim, wherein at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95% of said electrodes are connected to both a DC and an AC or RF voltage supply.

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76. A mass spectrometer as claimed in any preceding claim, wherein axially adjacent electrodes are supplied with AC or RF voltages having a phase difference of 180°.

5

77. A mass spectrometer as claimed in any preceding claim, further comprising an ion source selected from the group consisting of: (i) an Electrospray ("ESI") ion source; (ii) an Atmospheric Pressure Chemical Ionisation ("APCI") ion source; (iii) an Atmospheric Pressure Photo Ionisation ("APPI") ion source; (iv) an Inductively Coupled Plasma ("ICP") ion source; (v) an Electron Impact ("EI") ion source; (vi) an Chemical Ionisation ("CI") ion source; (vii) a Fast Atom Bombardment ("FAB") ion source; (viii) a Liquid Secondary Ions Mass Spectrometry ("LSIMS") ion source; (ix) a Matrix Assisted Laser Desorption Ionisation ("MALDI") ion source; and (x) a Laser Desorption Ionisation ("LDI") ion source.

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78. A mass spectrometer as claimed in any of claims 43-77, wherein said one or more transient DC voltages or said one or more transient DC voltage waveforms pass in use along said ion trap with a velocity which: (i) remains substantially constant; (ii) varies; (iii) increases; (iv) increases then decreases; (v) decreases; (vi) decreases then increases; (vii) reduces to substantially zero; (viii) reverses direction; or (ix) reduces to substantially zero and then reverses direction.

25

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79. A mass spectrometer as claimed in any preceding claim, wherein in use pulses of ions emerge from an exit of said ion trap.

5 80. A mass spectrometer as claimed in any preceding claim, wherein in use a complex mixture of ions are trapped within said ion trap.

10 81. A mass spectrometer as claimed in claim 80, wherein said complex mixture comprises at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 55, 60, 65, 70, 75, 80, 90, 95, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950 or 1000 different species of ions, each species of ions having a substantially
15 different mass to charge ratio.

20 82. A mass spectrometer as claimed in claim 80 or 81, further comprising a Matrix Assisted Laser Desorption Ionisation (MALDI) ion source.

25 83. A mass spectrometer as claimed in any preceding claim, wherein a complex mixture of ions is fractionated along the length of said ion trap and wherein each fraction is stored in a separate axial trapping region.

30 84. A mass spectrometer as claimed in claim 83, wherein ions are ejected or allowed to exit from one or more axial trapping regions as desired for subsequent mass analysis or for further experimentation.

85. A mass spectrometer as claimed in claim 84, wherein further experimentation comprises fragmentation and/or

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~~mass to charge ratio separation and/or ion mobility separation.~~

86. A method of mass spectrometry comprising:

5 providing an ion trap comprising a plurality of electrodes wherein at a first time t_1 ions enter said ion trap; and

forming or creating a plurality of trapping regions at a second later time t_2 along the length of said ion trap.
10

87. A method of mass spectrometry comprising:

providing an ion trap comprising a plurality of electrodes;

15 receiving ions within said ion trap;

trapping said ions in one or more axial trapping regions within said ion trap;

translating said one or more axial trapping regions along at least a portion of the axial length of said ion trap with an initial first velocity; and
20

progressively reducing said first velocity to a velocity less than 5 m/s.

88. A method of mass spectrometry comprising:

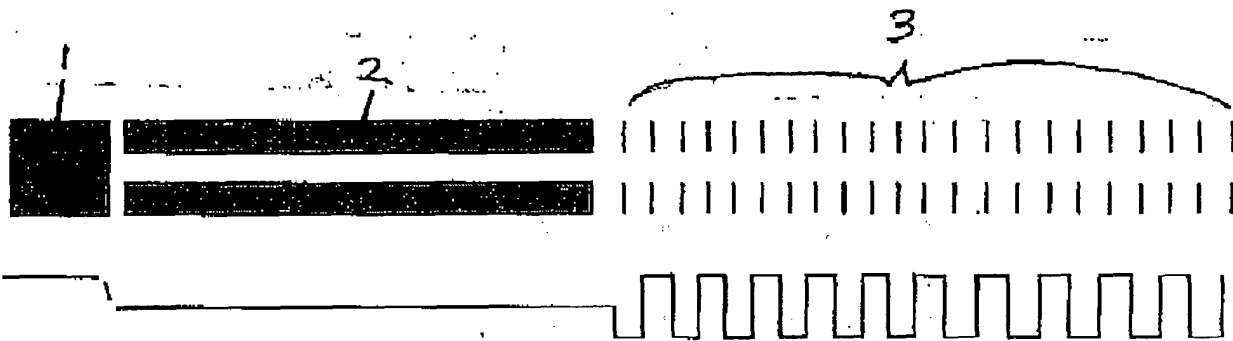
25 providing an ion trap comprising a plurality of electrodes;

receiving ions within said ion trap;

trapping said ions in one or more axial trapping regions within said ion trap;

30 translating said one or more axial trapping regions along at least a portion of the axial length of said ion trap with an initial first velocity; and

progressively reducing said first velocity to zero.



Electrical Potential Profile

Fig. 1



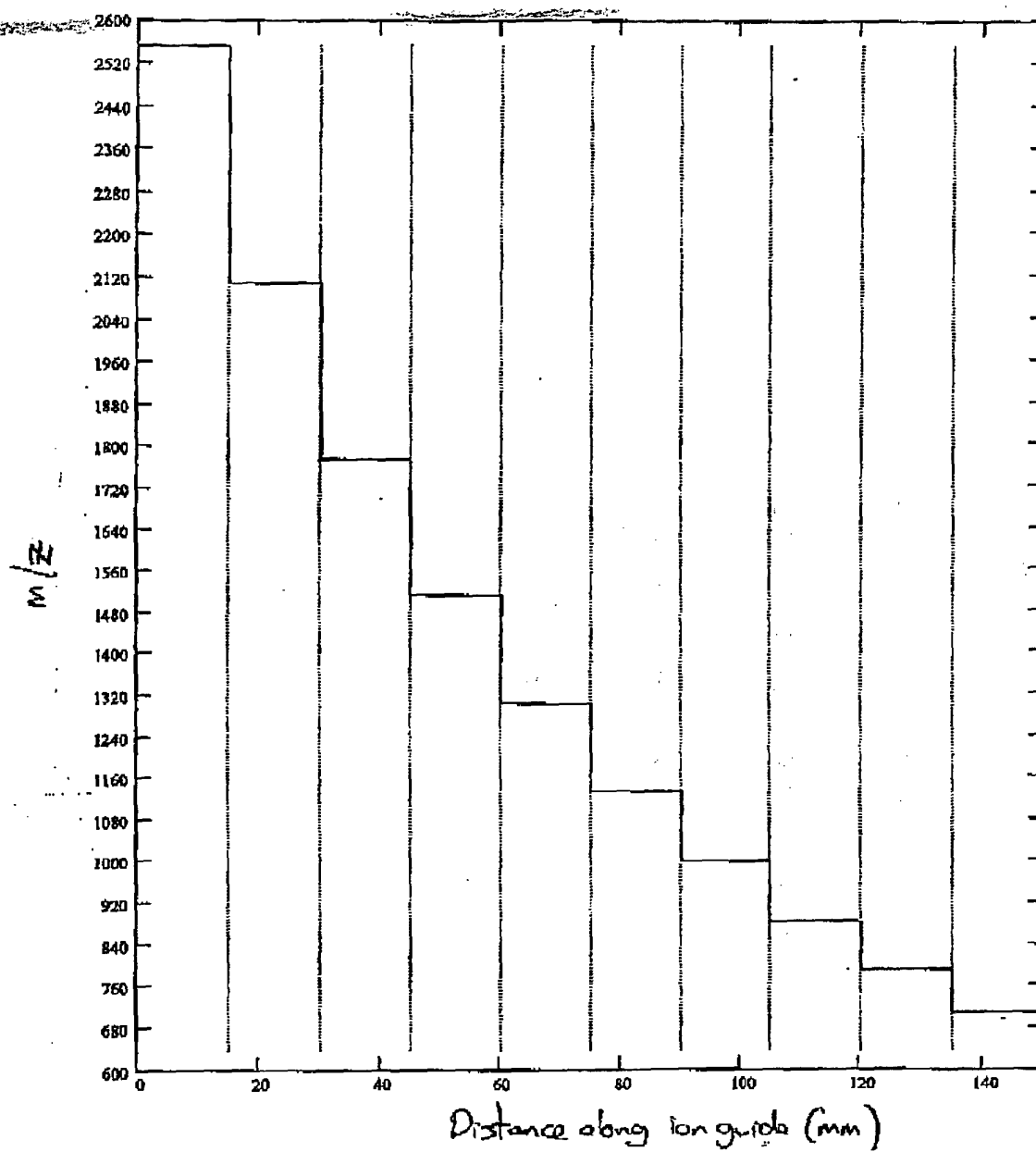


Fig. 2



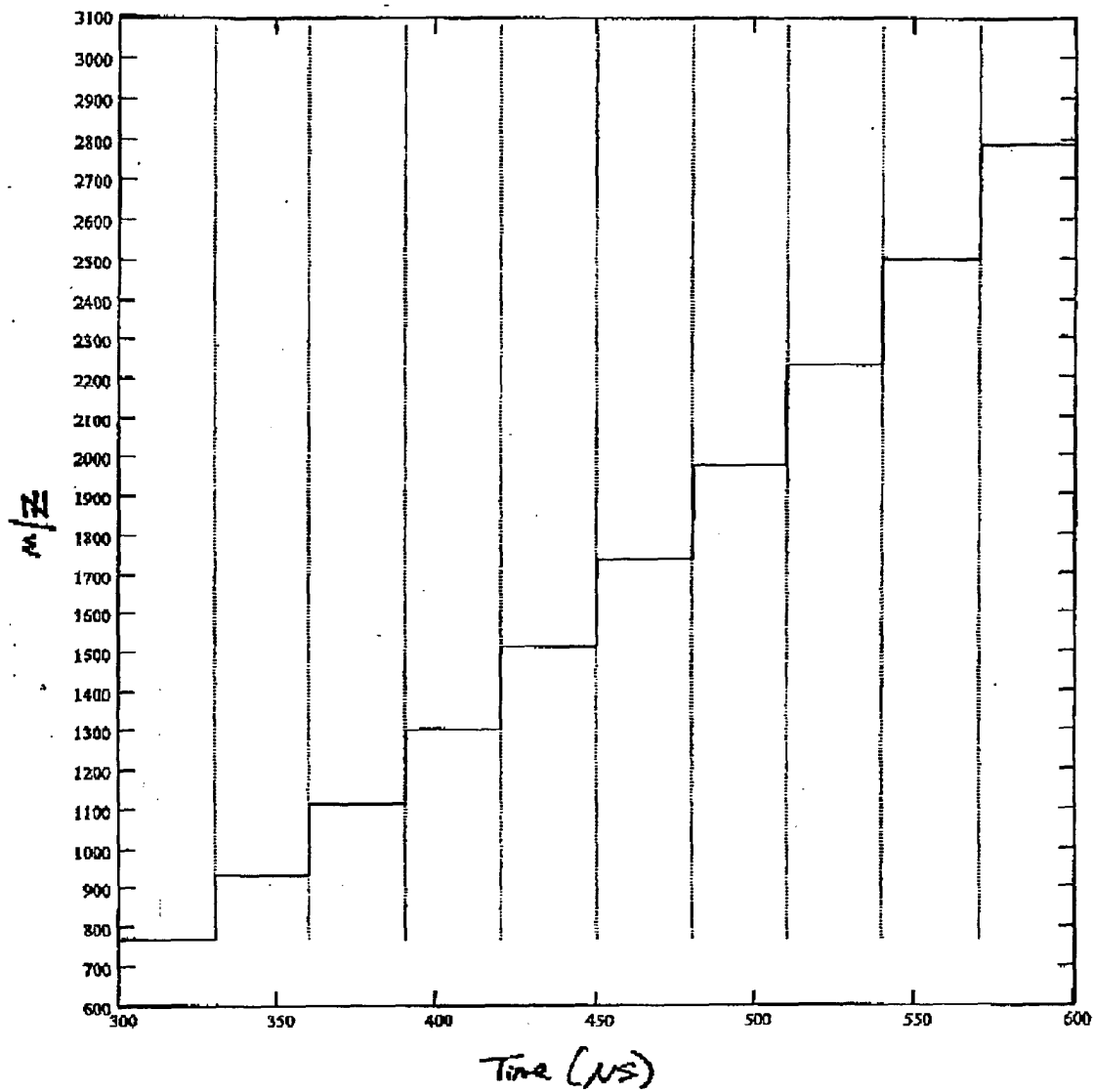


Fig. 3

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